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REPORT

CD NO.

COUNTRY	USSR
SUBJECT	Scientific - Medical, virus infections
HOW PUBLISHED	Thrice-monthly periodical
WHERE PUBLISHED	Moscow/Leningrad
DATE PUBLISHED	11 Aug 1950
LANGUAGE	Russian

DATE OF INFORMATION 1950

DATE DIST. 15 Jun 1951

NO. OF PAGES 5

50X1-HUM

SUPPLEMENT TO REPORT NO.

THIS IS UNEVALUATED INFORMATION

SOURCE Doklady Akademii Nauk SSSR, Vol LXXIII, No 5, pp 1049-1052.

SOME LAWS GOVERNING THE ACTION OF SUPPRESSORS OF VIRUSES AND BACTERIOPHAGE

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[Tables and figure referred to are appended.]

Since 1940 we have carried on an investigation dealing with inhibiting effects which various substances exert on enzymatic processes, thereby suppressing the propagation of a virus in an organism that is sensitive to these processes. In the course of this work, we discovered a whole series of substances which are capable of suppressing the virus of tobacco mosaic (1). It turned out later that some of these substances also suppress the reproduction of bacteriophage and phagolysis (2, 3). Some of the results of the work on the subject are listed in Table 1.

It can be seen from Table 1 that dinitrophenol suppresses the reproduction of tobacco mosaic virus (VTM). This fact, which was discovered by us in 1944 (4), can be correlated with the capacity of dinitrophenol to inhibit nuclein metabolism (5). Dinitrophenol also inhibits the reproduction of bacteriophage (3), but because this phenomenon is accompanied by a suppression of the propagation of bacteria, an inhibition of the bacteriophage as such could not be observed. The inhibitor also does not exert an absolute effect in a number of other cases, because it is poisonous to the host harboring the virus.

Acridine derivatives in a dilution of 1×10^{-5} suppress the propagation of Streptococcus lactis, while in a dilution of 5×10^{-6} they do not prevent the propagation of bacteria, but inhibit the bacteriophage. It is more difficult to demonstrate the capacity of acridine derivatives to suppress the bacteriophage of Staphylococcus aureus, because here the doses which are toxic to the bacteria and the bacteriophage, respectively, differ from each other to only an insignificant extent (6). By testing a large number of acridine derivatives, it was

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possible to select some which primarily suppress the bacteriophage in this case. Thus, nitroquinacrine exhibits only a low toxicity toward Staphylococcus aureus, but in a concentration of 3×10^{-4} suppresses bacteriophage. An inhibiting effect of harmine derivatives on VTM could not be observed, because this class of substances is too toxic toward tobacco leaves.

The examples cited above demonstrate that the rule in regard to the chemotherapeutic index applies to virus inhibitors as well (7).

It is not always the toxic effect which limits the application of the inhibitor, however. For instance, thiamin, which has a very low toxicity both with reference to tissues of higher plants and bacteria, suppresses VTM very actively, and is ineffective against bacteriophage. This type of activity is connected with some specific property of the virus. Very different from this type of specific inhibitor are acridine derivatives, which are practically universal virus inhibitors. This property of acridine derivatives, first established by us in the case of VTM (8, 9), later also became known with respect to bacteriophage, vaccine virus (10), the psittacosis group (11), and influenza (12). Quinacrine /atebrin/ was even applied in the treatment of influenza (13, 14).

We and our collaborators have tested a considerable number of acridine derivatives with respect to their action on VTM and bacteriophages, paying attention to the dependence of the inhibiting effect on chemical constitution. We found that acridines having a free amino group exhibit the strongest activity. They alone suppress VTM, while derivatives which contain substituents in the amino group, as, for instance quinacrine, are inactive against VTM. While derivatives which contain constitutents in the amino group have an antibacteriophage action, a high concentration is required in order that this action be exerted, and the effect is less strongly expressed than with acridine derivatives having a free amino group. Quinacrine, which has a chlorine in position 6, suppresses the bacteriophage of Streptococcus lactis, while the 5-chloro analog of quinacrine does not have that effect.

It is interesting that the 5-chloro analog also does not exhibit any antimalarial activity (15). Together with A. M. Movesesyan and T. P. Ovcharova, we demonstrated that various antimalarials which are analogous to quinacrine, but have a quinoline rather than acridine nucleus, lack the ability to suppress VTM or bacteriophage. This proves that the acridine nucleus is essential for the virus-inhibiting effect, while it is not of particular importance from the viewpoint of suppressing the malaria plasmodium. Paludrine and related compounds do not suppress VTM or bacteriophage.

The majority of virus inhibitors are cationic; erythrosin is the only example of an anionic virus inhibitor. The significance of the ionic character of cationic inhibitors is demonstrated by the fact that their activity is suppressed by Mg^{++} and Ca^{++} ions. The action of acridine derivatives or harmine derivatives may also be suppressed by nucleic acid, with which these substances form insoluble precipitates. Formation of these precipitates does not explain the virus-inhibiting effect by itself, however, because quinine, comachin, santochin, and other compounds form insoluble nucleic acid salts without exhibiting any virus-suppressing or bacteriophage-inhibiting activity whatever.

Our work has established that acridine derivatives form insoluble compounds with VTM, and that these compounds are destroyed in the course of dialysis (16). The anionic inhibitor erythrosin inactivates VTM and VTM is then reactivated by dialysis, showing that a loose bond, possibly of the salt type, is formed (17). The inactivation of VTM or bacteriophage by the inhibitors discussed here takes place in vitro only when large doses of the inhibitor are applied. This can be seen clearly in the experiments which we carried out with A. M. Movsesyan. A 24-hour-long contact of bacteriophage with rivanol does not lead to a significant

drop in the bacteriophage's titer, but after incubation of bacteriophage together with bacteria in the presence of rivanol the titer drops sharply. Figure 1 shows that a concentration of rivanol which does not affect the growth of bacteria not only prevents the propagation of bacteriophage, but leads to its progressive inactivation. This is something that is not observed in vitro. Similar relationships were established by studying the suppression of bacteriophage by harmine derivatives. By analogy with the bacteriostatic effect of chemotherapeutic agents, one may speak of the phagostatic effect of inhibitors.

Table 2 shows that cells of higher plants, bacteria, and the largest and most highly organized viruses (those of the psittacosis group) are sensitive to all of the substances tested. Rickettsiae exhibit peculiar behavior in that they are not inhibitated by sulfa drugs, but are actually stimulated by this class of substances as far as their propagation is concerned. Cysticetae (filterable bacteria) apparently are sensitive only to streptomycin. On the other hand, the virus of influenza vaccine, VTM, and bacteriophage are sensitive to acridine derivatives only. Acridine derivatives seem to be inhibitors exerting the most universal type of action, which probably is due to the fact that they affect the most fundamental biochemical processes, i.e., processes which are common to all of the organisms discussed here. One may assume that they suppress the enzymatic functions of some derivatives of nucleic acids, inhibiting the transfer of phosphorus and of hydrogen effected in the cell by these derivatives.

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Table 1. Inhibitors of VTM and Bacteriophage

Inhibitor	VTM	Bacteriophage of Bac. Coli	Bacteriophage of Streptococcus Lactis	Bacteriophage of Staphylococcus Aureus
Thiamin	+	-	-	-
Dinitrophenol	+	-		
Neutral red	+	+	-	+
Erythrosin	+	-	-	+
Harmine derivatives	-	-	+	+
Acridine derivatives	+	+	+	+

NOTE: A plus sign indicates positive inhibiting action while a minus sign denotes absence of such action.

Table 2. Action of Various Substances on the Propagation of Viruses, Bacteria, and Cells of Higher Organisms

Test Object	Acridine Derivatives	Sulfa Drugs	Penicillin	Streptomycin
Onion cells	+	+	+	+
Bacteria	+	+	+	+
Viruses of psittacosis group	+	+	+	+
Rickettsiae	+	-	+	+
Cysticetae		-	-	+
Virus of influenza vaccine	+	-	-	-
Bacteriophage	+	-	-	-
VTM	+	-	-	-

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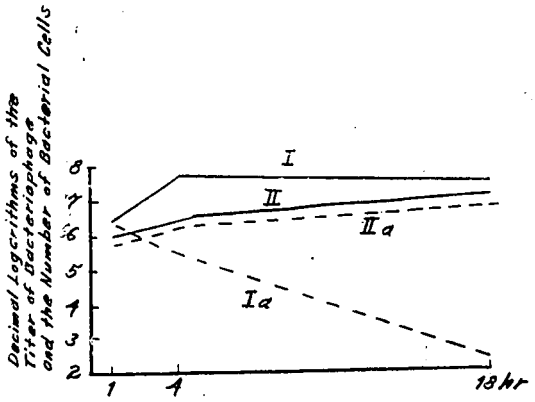

Figure 1. Titer of Bacteriophage and Quantity of Cells of Streptococcus Lactis in One Milliliter in Experiments on the Action of Rivanol. Solid lines indicate control experiments, broken lines experiments with rivanol. I, curve of the alteration of bacteriophage titer. II, curve showing increase of the number of bacterial cells.

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